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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,430	06/22/2006	Michael F. Tweedle	57637-1362	3664

35743 7590 05/04/2009

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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	**PAPER NUMBER**
1624	

NOTIFICATION DATE	DELIVERY MODE
05/04/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

klpatent@kramerlevin.com

Office Action Summary	Application No.	Applicant(s)	
	10/584,430	TWEEDLE ET AL.	
	Examiner	Art Unit	
	NOBLE JARRELL	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-39* is/are pending in the application.

4a) Of the above claim(s) *35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/22/2006;3/4/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I in the reply filed on 16 January 2009 is acknowledged. The traversal is on the ground(s) that groups I-III can be searched together. This argument is not found persuasive because groups II and III require an additional search based on the method of using a compound of claims 24-27 and the presence of a therapeutic agent linked to the 1,4,7,10-tetraazacyclododecane. In addition, it is unclear to which variable a therapeutic agent will be attached. None of the variables in claim 25 provide for a therapeutic agent.

The requirement is still deemed proper and is therefore made FINAL.

2. As a result of the election of group I, claims 24-34 are being examined on the merits.

3. Claims 35-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 36-38 have been withdrawn because an additional search is required for the therapeutic medium of claim 36 and a targeting moiety, diagnostic moiety, or therapeutic moiety (of claims 37 and 38). The additional component required may also control classification of the invention. Applicant timely traversed the restriction (election) requirement in the reply filed on 16 January 2009.

Claim Objections

4. Claims 25-26 and 28-34 are objected to because of the following informalities: The possibility "$CHP(O)(OH)_2,(CH_2)_n\text{-}NH_2$" for variable R^6 in claim 25 and R^5 in claim 26 appears to be incorrect. Examiner has interpreted this to be "$CHP(O)(OH)_2\text{-}(CH_2)_n\text{-}NH_2$". If this interpretation is wrong, applicants are encouraged to inform the examiner. Appropriate correction is required.

5. Claim 28 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in

independent form. Claim 28 fails to further limit claims 24-27 because it is unclear where the multimer is being formed relative to a polyazamacrocyclic compound with at least one phosphonic group, a compound of formula II, or a compound of formula IV.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 24 and 28-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants do not have possession of the entire genus of compounds represented by claim 24. Since claim 28-34 are dependent on this claims, these claims are rejected as well.

Claims 24 and 28-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 24 and 28-34 do not contain generic formulae indicating structural makeup for the polyazamacrocyclic ring that is part of applicants' invention. In the broadest reasonable interpretation of claim 24, a polyazamacrocyclic compound can be as simple as any ring (aromatic or non-aromatic) with at least two nitrogen atoms. Thus, claim 24 is interpreted as any compound comprising a ring with at least two nitrogen atoms and a phosphonic group. Claim 24 is not clear how the phosphonic group is attached to the ring portion of the compound. Claim 24 has been examined in relation to the scope of the elected group and species.

However, applicants have not shown they are able to prepare this compound. Examples 1-13 (pages 33-61 of the specification) show that applicants have possession only for 1,4,7,10-tetraazacyclododecane rings with at least one phosphonic-methylene group attached to a nitrogen atom within the ring.

According to the MPEP §2163 I. A. "the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." The MPEP states in §2163 II 3 ii) "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406."

According to the MPEP §2163.02 Standard for Determining Compliance With the Written Description Requirement, "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter". Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))."

This case was filed before Applicants had a clear idea of the structures encompassing the scope of claims 24 and 28-34, other than the specific compounds recited in claim 27 and compounds embraced by formulae II and IV. The specification provides broad areas of future research and speculation, inviting undue experimentation in learning how to use Applicants' invention.

Applicants are reminded of what the U.S. Court of Appeals Federal Circuit wrote in University of California v. Eli Lilly and Co. 43 USPQ2d 1398, "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). "It is only a definition of a useful result rather than a definition of what achieves that result." "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.")".

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 25-26 and 28-34 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 25-26 and 28-34 are unclear because the connectivity of the "Aryl-NHCS" group (last possibility for variable X of claim 25 and R^5 of claim 26) is unclear. How is this group attached to the CH group? Is it possibility one, CH-CSNH-aryl, or possibility two, CH-aryl-NHCS? If the connection is possibility two, the octet of the carbon atom is not fulfilled (it is trivalent).

10. Claim 28 recites the possibility of compounds of claims 24-27 existing as multimers. There is insufficient antecedent basis for this limitation in the claim. In each of these claims, it is unclear how the second (and higher) unit(s) is (are) attached to the first unit. None of the variables in claims 24-27 provides clear interpretation as to how the other units are attached.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 24 and 29-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Huskens et al. (*Inorganic Chemistry*, **1997**, *36*, 1495-1503, cited in IDS). Huskens et al. teach the preparation of DO2A-EP (page 1495) and gadolinium, magnesium, and calcium chelates thereof (page 1499). In DO2A-EP, the ring is 1,4,7,10-tetrazazcyclododecane. In this compound, the nitrogen atoms are substituted as follows: nitrogen atoms 1 and 7 are substituted with a CH_2CO_2H group; nitrogen atom 4 is substituted with a $CH_2P(O)(OEt)(OH)$ group; and nitrogen atom 10 is substituted with $CH_2P(O)(OH)_2$ group. These compounds are useful as magnetic resonance imaging (MRI) agents, diagnostic agents, and radiotherapeutic agents (page 1495).

13. Claims 24-25, 27, and 29-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Ranganathan et al. (WO 95/31444, published 23 November 1995, cited in IDS). Ranganathan et al. teach example 10 (pages 57-59). In this example, both the compounds and its corresponding gadolinium chelate are taught. The compound is a 1,4,7,10-tetraazacyclododecane ring substituted by three CH_2CO_2H groups (at nitrogen atoms 1, 4, and 10) and one $CH_2P(O)(OH)_2$ (at nitrogen atom 7). Step A of example 10 teaches the preparation of the compound (this compound is the first compound listed in claim 27). Step B teaches the preparation of the gadolinium salt. This compound is useful as an imaging, diagnostic, and radiotherapeutic agent (page 14, lines 19-32).

14. Claims 24-25, 27, and 31-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Zimova et al. (*Czechoslovak Journal of Physics*, **2003**, *53*, pages A803-A808, available January 2003, cited in IDS). Zimova et al. teach compound P2 (page A804). This compound has a 1,4,7,10-tetraazacyclododecane ring substituted by three CH_2CO_2H groups (at the 1, 7, and 10 nitrogen atoms) and one $CH_2P(O)(OH)_2$ group (on the 4-nitrogen atom of the ring) (this compound is the first compound listed in claim 27). This compound is useful as a diagnostic, radiotherapeutic, or radioimmunotherapeutic agent (page A803).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. Claims 25, 27, and 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ranganathan et al. (WO 95/31444, published 23 November 1995, cited in IDS).

Determining the scope and contents of the prior art

Ranganathan et al. teach example 10 (pages 57-59). In this example, both the compounds and its corresponding gadolinium chelate are taught. The compound is a 1,4,7,10-tetraazacyclododecane ring substituted by three CH_2CO_2H groups (at nitrogen atoms 1, 4, and 10) and one $CH_2P(O)(OH)_2$ (at nitrogen atom 7). Step A of example 10 teaches the preparation of the compound. Step B teaches the preparation of the gadolinium salt. This compound is useful as an imaging, diagnostic, and radiotherapeutic agent (page 14, lines 19-32).

Ascertaining the differences between the prior art and the claims at issue

In the instant application, variable R6 can be a $CH(Me)P(O)(OH)_2$ group. In the prior art, variable R6 is $CH_2P(O)(OH)_2$. The difference between these two groups is the existence of a CH_2 versus a CH(Me) group.

Resolving the level of ordinary skill in the pertinent art

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds of the claims 24-27.

Considering objective evidence present in the application indicating obviousness or nonobviousness

Ranganathan et al. teach that a compound of example 10 is useful as an imaging, diagnostic, and radiotherapeutic agent.

In re Lohr and Spurlin (137 USPQ 548) teaches:

> When a new compound so closely related to a prior art compound to be structurally obvious is sought to be patented, clear and convincing evidence of substantially greater effectiveness is needed.

In a comparison of the instant application and the prior art, one of ordinary skill in the art expects a reasonable expectation of success because the only difference between the two compounds is a CH_2 and CH(Me) group. The final product of example 10 works in the same field of study as the second compound of claim 27. Thus, in this class of compounds, a hydrogen atom is considered an analogue of a methyl group.

18. Claims 25, 27, and 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimova et al. (*Czechoslovak Journal of Physics*, **2003**, *53*, pages A803-A808, available January 2003, cited in IDS) in view of Ranganathan et al. (WO 95/31444, published 23 November 1995, cited in IDS).

Determining the scope and contents of the prior art

Zimova et al. teach compound P2 (page A804). This compound has a 1,4,7,10-tetraazacyclododecane ring substituted by three CH_2CO_2H groups (at the 1, 7, and 10 nitrogen atoms) and one $CH_2P(O)(OH)_2$ group (on the 4-nitrogen atom of the ring). This compound is useful as a diagnostic, radiotherapeutic, or radioimmunotherapeutic agent (page A803).

Ranganathan et al. teach example 10 (pages 57-59). In this example, both the compounds and its corresponding gadolinium chelate are taught. The compound is a 1,4,7,10-tetraazacyclododecane ring substituted by three CH_2CO_2H groups (at nitrogen atoms 1, 4, and 10) and one $CH_2P(O)(OH)_2$ (at nitrogen atom 7). Step A of example 10 teaches the preparation of the compound. Step B teaches the preparation of the gadolinium salt. This compound is useful as an imaging, diagnostic, and radiotherapeutic agent (page 14, lines 19-32).

Ascertaining the differences between the prior art and the claims at issue

In the instant application, variable R6 can be a $CH(Me)P(O)(OH)_2$ group. In the prior art, variable R6 is $CH_2P(O)(OH)_2$. The difference between these two groups is the existence of a CH_2 versus a CH(Me) group.

Resolving the level of ordinary skill in the pertinent art

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds of claims 24-27.

Considering objective evidence present in the application indicating obviousness or nonobviousness

Zimova et al. et al. teach that compound P2 is useful as an imaging, diagnostic, and radiotherapeutic agent.

In re Lohr and Spurlin (137 USPQ 548) teaches:

> When a new compound so closely related to a prior art compound to be structurally obvious is sought to be patented, clear and convincing evidence of substantially greater effectiveness is needed.

In a comparison of the instant application and the prior art, one of ordinary skill in the art expects a reasonable expectation of success because the only difference between the two compounds is a CH_2 and CH(Me) group. The final product of example 10 works in the same field of study as the second compound of claim 27. Thus, in this class of compounds, a hydrogen atom is considered an analogue of a methyl group. It is important to note that the product of step A of example 10 in Ranganathan et al. and compound P2 are the same compound. Based on the teaching of Ranganathan, compound P2 of Zimova et al. can be made into a gadolinium salt.

Double Patenting

19. Claim 34 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 33. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other

as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 34 is a duplicate of claim 33 because the intended use for the kit does not carry any patentable weight.

Conclusion

20. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624